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# Adjuvant Treatment of Colorectal Cancer

## A Review

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*Surgical operation remains the most effective method of treatment for patients with cancer of the large bowel. However, innovative surgical techniques have not improved survival rates for colorectal cancer in 25 years.*

*Attempts at increasing survival with chemotherapy as an adjunct to surgical procedures remain inconclusive and controversial. Many adjuvant chemotherapy trials have failed to recognize those prognostic factors—such as nodal involvement, serosal penetration, vascular or perineural invasion, and microscopic invasion at margins of resection—that characterize certain patients at high risk for recurrent cancer. Failure to include only high risk patients in adjuvant chemotherapy is, in part, responsible for the lackluster performance to date.*

*For rectal cancer, preoperative irradiation increases the chances of cure with surgical operation by reduction of pathologic staging, but it has not increased survival in patients with persistent nodal involvement.*

*Immunotherapy is a possibly valuable method of treatment; however, it is clinically untested. An adjuvant immunotherapy protocol for high risk patients is described.*

THE ONLY ACCEPTABLE curative therapy for invasive adenocarcinoma of the large bowel continues to be radical surgical excision.[1] Unfortunately newer surgical techniques and manipulations have not improved five-year survival rates for more than two decades.[2] Previous attempts to prolong survival by employing radiation (excluding perhaps preoperative irradiation for rectal cancer) and chemotherapy, either as preoperative or as postsurgical adjuvants, have not yet been successful. It is now believed that adjuvant therapies may be effective in subgroups of patients defined by the presence or absence of risk factors. If so, the role of immunomanipulation also holds promise of significance. This paper summarizes previous adjuvant approaches for treatment of large bowel cancer in order to crystallize the rationale for adjuvant therapy including immunomanipulation.

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CMI = cell-mediated immunity
COG = Central Oncology Group
5-FU = 5-fluorouracil
Me-CCNU = 1-(2-chlorethyl-3-4 methylcyclohexyl)-1-nitrosourea
MER = methanol extracted residue of BCG
VASAG = Veterans Administration Surgical Adjuvant Group
WCSG = Western Cancer Study Group

## Adjuvant Radiation Therapy in Rectal Cancer

Radiation therapy for patients with unresectable primary large bowel cancer or a local recurrence has been shown to have significant palliative effects.[3,4] It has been postulated that preoperative irradiation to rectal and low sigmoid cancer would improve chances of survival.[5-7] A retrospective survival study of 1,700 previously untreated patients with rectal cancer has been reported from Memorial Hospital in New York. With the use of preoperative radiation therapy there was a significant increase in the five-year survival rate (37 percent) over that for surgical procedures alone (23 percent) in patients who had lymph node involvement only.[1,8-10] Results of a partially randomized prospective study subsequently showed that in cases of lymph node involvement treated with surgical operation alone there was a slightly increased proportion of patients surviving five years, compared with survival when both radiation therapy and surgical operation were used.[1,11,12]

Several reviews of the Veterans Administration Surgical Adjuvant Group's (VASAG) preoperative radiation protocol for rectal cancer show a 12 percent increase in five-year survival in only those patients receiving both radiation therapy and abdominoperineal resection. Concurrent randomized controls treated only surgically were used in these studies.[13-16] Preoperative irradiation was given in doses of 2,000 to 2,500 rads during two weeks. The current VASAG preoperative radiation therapy protocol utilizes 3,150 rads in 18 fractions randomly matched against no preoperative treatment.

The Central Oncology Group (COG) and the Radiation Therapy Oncology Group are conducting a study (COG No. 7240) comparing high (4,000-4,600 rads in four to five weeks) and low dose (2,000-2,500 rads in two weeks) preoperative radiation therapy in rectal cancer. Results in both groups of patients will be compared with findings in a group that received no preoperative treatment.

The European Organization for Research on Treatment of Cancer recommends use of 3,450 rads preoperatively over a 18-day period for rectal cancer. A comparison is being made with preoperative irradiation plus chemotherapy with 5-fluorouracil (5-FU).[15]

The above-cited studies permit certain conclusions concerning preoperative radiation therapy in rectal cancer: (1) Preoperative rectal irradiation reduces the frequency of lymph node involvement by about 13 percent.[13-16] By reducing pathologic stage, radiation therapy appears to increase chances of surgical cure even when low dose irradiation is used. (2) Preoperative rectal irradiation reduces local recurrence, regardless of pathologic staging.[15] (3) However, no randomized study has yet shown a survival benefit with preoperative radiation in patients in whom there continues to be nodal involvement at the time of operation.

## Factors Associated with Poor Prognosis in Large Bowel Cancer

One of the pitfalls that plagued earlier surgical adjuvant chemotherapy trials was a lack of awareness of those patient characteristics associated with a high probability of disease recurrence, regardless of the adequacy of the surgical resection.

Pathologic stage of the tumor has been shown to be a major prognostic factor according to Dukes:[17]

*A*—Cases in which the tumor has not penetrated the muscle wall of the bowel;
*B*—Cases in which tumor extends to the pericolic or perirectal tissues but has not reached the lymph nodes;
*C*—Cases in which tumor has metastasized to the proximal ($C_1$) or regional ($C_2$) lymph nodes, and
*D*—Cases in which tumor has metastasized to distant locations.

Survival at five years is:[18]

Dukes' *A*—60 percent to 80 percent;
Dukes' *B*—25 percent to 65 percent;
Dukes' *C*—6 percent to 28 percent;
Dukes' *D* involving liver or lung—less than 15 percent.

In addition to Dukes' staging, other poor prognostic indicators are:

- Presence of gross or microscopic blood vessel invasion in the resected primary specimen has been associated with 19 to 37 percent five-year survival.[19-21] In patients with vascular invasion, the probability of recurrent tumor is 74 percent.[22]
- Perineural involvement in the resected surgical specimen has been related to a 20 percent five-year patient survival.[21]
- Any combination of lymph node, vascular or perineural tumor infiltration has additive effects in terms of decreasing the chances of a five-year survival.[21]
- An exceedingly high rate of anastamotic recurrence is observed in patients in whom resection margins are not free of microscopic tumor foci.

In one review, first disease recurrence within 18 months of surgical operation was observed in more than 75 percent of patients in whom one of the above poor prognostic factors was seen.[23]

## Adjuvant Chemotherapy

Historically, adjuvant chemotherapy was used in an attempt to destroy cells left in the operative field and to prevent spread via the blood stream or lymphatics during surgical operation. Therefore, early studies employed short duration adjuvant therapy to irradicate the small pool of locally residual cancer cells. At first, local irrigation of the bowel ends with half-strength Dakin's solution or 1:500 perchloride of mercury was advocated.[24-28]

Systemic chemotherapy began with early randomized controlled studies testing effects of triethylenethiophosphoramide (thiotepa) and fluorodeoxyuridine (FUDR). Various routes of administration were used (intraperitoneal, mesenteric vein, intravenous) but were unsuccessful.[29-31]

Increased survival in patients with lymph node involvement was shown, compared with a retrospective control group not treated, when intraluminally given 5-FU and systemic administration of 5-FU two days postoperatively were used.[32] These observations have motivated the initiation of a randomized cooperative clinical study comparing results of intraluminally given 5-FU in combination with systemic administration of 5-FU after surgical operation with results of operation alone.[33]

In 1971 the VASAG reported on a randomized study of no treatment compared with 5-FU treated colon cancer patients.[34] 5-FU was given in the immediate postoperative period (14 days postresection) for five successive days at 12 mg per kg of body weight intravenously. Treatment assignment was not stratified by Dukes' classification or other prognostic variables influencing disease recurrence, but by the surgeon's opinion regarding potential for cure. All patients were followed for survival. Those patients who received surgical procedures termed "clinically palliative" and "clinically curative" received a second course of 5-FU six weeks later. There was no statistically significant difference in the five-year survival rate or the disease-free interval between treated and untreated populations in any of the patient groups. Furthermore, retrospective analysis by Dukes' classification again failed to show that therapy with 5-FU achieved survival rates superior to those of control populations. The five-year survival rate for patients (308) undergoing "curative resection" was 58.5 percent for treated patients (142) versus 49.4 percent for control patients (166). The trend of this study appears to favor 5-FU treatment, but statistical significance is lacking.[35] Thus, findings in early trials utilizing thiotepa, FUDR and 5-FU have failed to show significant prolongation in survival. Doses, schedules, route of administration, the short duration of adjuvant treatment and disregard for prognostic factors in treatment assignment may be important factors in this failure.

The advocation of prolonged intermittent systemic adjuvant chemotherapy came about with the realization that (1) occult metastatic cancer sites can exist at the time of surgical operation and do not result exclusively from surgical manipulation and (2) repeated courses of treatment are necessary to irradicate this small residual tumor cell burden.

Prolonged intermittent 5-FU adjuvant therapy is being tested in a randomized prospective study by the Central Oncology Group.[36] Before random assignment to groups receiving adjuvant 5-FU therapy or no treatment, patients with poor prognosis are classified as "curative" or "palliative" resection. Poor prognosis in the curative group includes the following factors: (1) positive lymph nodes, (2) serosal penetration or invasion of perirectal fat, (3) blood vessel invasion, (4) lymphatic invasion and (5) cancer in other organs removed as part of the resection.

In this study, 5-FU was given intravenously at 12 mg per kg of body weight per day for four days and then 6 mg per kg of body weight every other day for five doses or to toxicity. Following

this induction course, 5-FU was given weekly at 12 mg per kg of body weight for one year. Endpoints were first disease recurrence and death.

The follow-up period is still relatively short but at last report 49 of 64 patients (77 percent) classified as "curative" resection were disease-free after treatment with 5-FU, as compared with 42 of 63 patients (67 percent) similarly classified and assigned to no treatment.[36] For both curative and palliative resected patients 5-FU treatment has not shown significant superiority over no treatment with respect to disease-free interval or five-year survival.

The VASAG has also investigated prolonged intermittent chemotherapy (5-FU) in colon cancer. Chemotherapy was given in the same manner as in their previous study[34] but was repeated every six weeks for 18 months. Case accrual terminated in August 1973. To date, no difference has been shown in patient survival associated with prolonged 5-FU treatment.[35]

Lawrence has recently reported no significant treatment benefit, regardless of stage, with 5-FU used as a prolonged intermittent postoperative (one year) adjuvant in colorectal cancer patients. Treatment benefit was measured in terms of disease-free interval and survival.[37]

Other nonrandomized studies showing significant superiority of 5-FU over no treatment continue to be reported in the literature.[38] The success of adjuvant 5-FU chemotherapy in prolonging patient survival can not be determined by retrospective comparison with control populations.

The recent reports of higher than anticipated regression proportions in metastatic colon cancer when drugs with low individual activity are combined have prompted these drug combinations to be considered as adjuncts to surgical operation.[39-42] The use of combination chemotherapy as adjuncts to surgical operation adds further risk of systemic toxicity, difficult patient management, interference with patient quality of life and potentially greater immune "paralysis" (tolerance) to residual tumor burden. In spite of these potential difficulties, several cooperative groups have initiated studies using combination chemotherapy (namely Me-CCNU [that is, 1-(2-chlorethyl-3-4 methylcyclohexyl)-1-nitrosourea] plus 5-FU) as an adjunct to surgical operation.

## Immunotherapy as Adjuvant Treatment

Many investigators have theorized the clinical use of immunomanipulation may be effective only at the time of minimal tumor burden because host immune "paralysis" increases with increasing tumor burden.[43] Reactive regional lymph node hyperplasia with germinal center proliferation draining a primary malignancy has been observed in both breast and colon cancer.[44-47] This suggests a host immune response to the tumor. Postoperative irradiation of regional draining lymph nodes in breast cancer has been a common practice and now has been associated with decreased survival when compared with nonirradiated postoperative controls.[48] This disturbing observation perhaps reflects the result of lymph node destruction secondary to radiation therapy, thus "paralyzing" an important defense against dissemination. It is conceivable that chemotherapy may act similarly to cause both regional and systemic lymph node immunosuppression and permit enhanced tumor growth.

Implementation of nonspecific immunotherapy at the time of minimal tumor burden will theoretically stimulate cell-mediated immunity (CMI) and increase the intensity of low level antitumor immune responses leading to tumor rejection. The cells involved in this CMI anticancer effect include macrophages, lymphocytes, polymorphonuclear leukocytes and, to some extent, plasma cells. Some or all of these cell types may be stimulated by various immunotherapies. The degree of cellular response often depends on route of drug administration. In animal tumor systems the immunostimulants, Corynebacterium parvum or bacille Calmette Guérin (BCG) appear to have greater immunocytotoxicity to a cancer inoculum when given intravenously or intraperitoneally, as compared with subcutaneous administration.[49,50] It is postulated from animal data that the intravenous route is superior to the subcutaneous route because of direct visceral systemic stimulation by intravenous delivery rather than the regional lymph node hyperplasia which follows subcutaneous administration.

A randomized surgical adjuvant protocol for patients with colorectal cancer who have had "curative" surgical resections and in whom any one of the poor prognostic factors listed above is present has been designed by the Western Cancer Study Group (WCSG). The agents employed are immunostimulants: Corynebacterium parvum and levamisole. The WCSG chose C. parvum for several reasons: (1) It appears to be a potent anticancer immunostimulant in many animal tumors and even more effective than BCG in

identical immunoadjuvant animal tumor systems;[51,52] (2) C. parvum is formalin-fixed and not capable of transmitting active disease as is BCG, nor is it dependent on viable organisms for its immunostimulant properties, as is BCG; (3) C. parvum is not plagued with variation in organism viability within intrainstitutional and interinstitutional manufacturers, as is BCG; (4) C. parvum preparation does not show inconsistent dosage administration caused by cellular clumping within multidose vials as has been the case with BCG;[53] (5) in Phase II clinical trials, C. parvum has shown single agent antitumor effect in several metastatic tumor types.[54]

C. parvum toxicity has been established in Phase I trials. Side effects include pain at injection site, fever, malaise, flu-like syndrome and sensitivity to barbiturates when given subcutaneously.[55] In addition, severe chills, fever, hypotension and hypertension may be observed when the agent is administered intravenously.[56] Pain at subcutaneous injection sites can be obviated by mixing with xylocaine. Side effects tend to be more severe when C. parvum is given intravenously compared with subcutaneous injection.[57,58] The high fevers and chills are associated with large intravenous doses and are most severe with the first intravenous injection, diminishing with subsequent doses.[57,59] If initial intravenous doses are kept small and subsequent doses are slowly increased, these toxic effects diminish.[57,60]

Levamisole, an established antihelminthic, was discovered by Renoux and Renoux to possess immunostimulating properties in animals.[61] Since their initial work, many animal data have accumulated to confirm and extend these observations.[62] In human studies levamisole has been found to restore recall skin test antigens, and to increase *in vitro* lymphocyte reactivity.[63,64] In general, it appears that levamisole increases a low level of preexisting immunity rather than stimulating an immune response de novo. The mechanism by which this occurs may be macrophage stimulation via a serum factor (which is not the drug) found in levamisole-treated patients.[65] Although its performance as an antitumor agent in animal models appears to be less than C. parvum or BCG, findings in recent adjuvant studies by Rojas in patients with breast cancer and Amery in patients with lung cancer have shown increased disease-free intervals in these patients when compared with a randomized prospective treatment control group.[66,67] Such preliminary reports are exciting but remain to be clinically confirmed. When given as discontinuous therapy (that is, three days of oral administration every two weeks) side effects occur in about 5 percent of patients. They include central nervous system stimulation manifested by nervousness and insomnia; gastrointestinal complaints, such as nausea and vomiting, and skin rash. There has been no adverse effect on liver, kidneys or cardiac function recorded.

Further discussion of current information on other promising nonspecific immunostimulants such as BCG and methanol extracted residue of BCG (MER) is beyond the scope of this article. However, recent preliminary results have shown increased disease free interval for BCG treated colon cancer patients (Dukes' *C* stage) compared with historical controls. Even though historical controls have been used for treatment comparison such data help substantiate early implementation of immunotherapy in cancer of the large bowel.[68] Clinical trials of specific immunotherapy (for example, with transfer factor, immune ribonucleic acid (RNA), modified tumor antigens, cell wall extracts) are chiefly limited to single institution studies with small numbers of patients because of the large procurement and logistic problems.

## Proposed Immunoadjuvant Trials for Colon Cancer

Several cooperative group studies that will use both chemotherapy and immunotherapy in combination are presently undergoing development and activation. The Large Bowel Cancer Working Group has a protocol proposal prepared by Holyoke at Roswell Park Memorial Institute for "curative" postsurgical patients with adenocarcinoma of the colon. In this study there is randomization to four treatment arms: (1) control; (2) 5-FU plus Me-CCNU; (3) MER alone; (4) 5-FU plus Me-CCNU and MER. The VASAG has amended their current colon adjuvant protocol No. 27 for patients with histologically proven residual disease. These patients will be randomized to prolonged intermittent chemotherapy (5-FU plus Me-CCNU) with or without MER. Further details concerning these proposals are not available.

The Western Cancer Study Group has elected not to combine chemotherapy and immunotherapy in a surgical adjuvant study for colon cancer. This is based on several reasons: (1) there are no conclusive data that single or combi-

nation adjuvant chemotherapy prolongs disease-free interval or survival for large bowel cancer; (2) chemotherapy may entail additional systemic toxicity and potential for impairment of quality of life; (3) while chemotherapy may enhance host immunoreactivity to large volume malignancies, it also may "paralyze" established nodal defense systems against minimal tumor cell numbers; (4) combination chemotherapy when used in an adjuvant setting leaves few alternative chemotherapeutic drugs available at first disease recurrence; (5) chemotherapy could potentially be antagonistic to immunomanipulation; (6) information about dose, routes of administration and single agent effectiveness for immunostimulants should be established before combination with chemotherapeutic regimens.

The WCSG study employs immunotherapy only for adjuvant treatment of patients with totally resected colorectal carcinoma and poor prognostic indicators. The patients will be randomized to: placebo; levamisole; C. parvum given subcutaneously; C. parvum given intravenously. Disease-free interval, survival and side effects will be the endpoints of treatment effectiveness.

As in any large scale study assessing the effectiveness of adjuvant therapy, case accrual is a critical aspect. A study designed for long-term follow-up must encourage rapid case accrual. The WCSG invites any interested physicians seeking further information concerning this study and possible case referral to contact the authors. The WCSG is a multiinstitutional cooperative cancer study group with investigators throughout the western United States. Participating WCSG investigators are very willing to assist physicians in their area who have potential patients to enroll.

## Summary

An historical review of early treatment of large bowel cancer is presented. Several observations concerning the efficacy of single modality therapy can be made with regard to improving survival. (1) Since newer surgical techniques have not altered survival rates in 25 years, it appears that further surgical manipulation is unlikely to achieve future survival benefit. (2) Preoperative radiation therapy for rectal cancer both improves surgical curability by reducing pathological stage and reduces local recurrence; but it has not resulted in increased survival in patients with persistent nodal disease. (3) Short-term adjuvant chemotherapy is of no apparent value in increasing survival; prolonged intermittent adjuvant chemotherapy has not yet achieved increased survival. The use of combination chemotherapy as an adjunct to surgical operation is currently being evaluated and no data as to its efficacy are available. (4) The employment of immunotherapy as an adjunct to surgical operation is theoretically sound but clinically untested. Immunotherapy as proposed by the WCSG is described. If immunotherapy, chemotherapy or radiation therapy are proved to be effective in increasing survival in large bowel cancer then ultimately a multimodality approach may be adapted to further influence disease curability.

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